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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,471	11/04/1998	STEFAN ROSE-JOHN	012627-009	2240

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/142,471	ROSE-JOHN, STEFAN	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 April 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *20 April 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-4,7-9,11 and 12*.

   Claim(s) withdrawn from consideration: *5*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 3. Applicant's reply has overcome the following rejection(s): objection to claim 4 and rejection of claim 2 under 35 USC 112 second paragraph.

Continuation of 5. does NOT place the application in condition for allowance because: Applicant's arguments that the three criteria to establish a prima facie case of obviousness have not been met by the cited references, alone or in combination, have been fully considered but are not deemed persuasive. Applicant argues that Sui et al. discloses use of IL-6 and IL-6R separately, and does not disclose the claimed conjugate of the present invention, that the secondary reference, Wong et al., discloses a MCH molecule covalently bound to a peptide and does not correspond to a cytokine or receptor, neither of the references disclose or even suggest a conjugate comprising two polypeptides of cytokine and receptor, and there is no motivation to modify the recited references to arrive at the claimed invention.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Sui et al. teaches that the administration of this complex alone, or SCF alone, had little effect in increasing expansion of hemopoietic progenitor cells, while the combination of IL-6/IL-6R complex and SCF was more effective. Wong et al. is relevant, since the reference teaches that it is advantageous to make fusion proteins (for example, reducing the complex to a single molecule to avoid separate purifications, enhanced yields and stability, and effective positioning of the components of the fusion protein). Therefore, it would have been prima facie obvious to one of ordinary skill in the art to make a fusion protein, as taught by Wong et al., comprising IL-6 and IL-6R, since administration of a IL-6/IL-6R complex along with SCF increases expansion of progenitor cells, as taught by Sui et al., and a fusion protein comprising IL-6 and IL-6R would have advantages over administration of the separate proteins, as taught by Wong et al.

Applicant further submits on page 7 of the response that surprising and unexpected results are present with respect to the present invention, and that the fusion polypeptide had increased activity over the single polypeptides. Applicant points to Example 5 of the specification and asserts that the result shows that the expansion of the colony formation of CD34+ cells can be increased by 300% compared to the separate addition of IL-6 and IL-6 receptor. Applicant also points to Example 4 on pages 7-8 of the response, in which the haptoglobin expression in a hepatoma cell line is stimulated to a greater extent as compared to that resulting from the separate addition of IL-6 and IL-6R, and as further support, submit that the fusion polypeptide of the present invention is capable of regenerating diseased liver tissue which can not be achieved by application of the single polypeptide.

Applicants' arguments have been fully considered but are not deemed persuasive. First, in example 5, there was no sIL-6 added to the cells, and there was only a comparison between the fusion protein and IL-6. Secondly, in Example 4, it is not an unexpected result that the fusion protein would be more effective than the single polypeptides. The fusion polypeptide would be more stable, and would present the IL-6 and sIL-6 in a specific active conformation and in a 1:1 stoichiometric ratio, and one of ordinary skill in the art would expect such a fusion protein to be at least as effective and probably more effective than administration of the single polypeptides. Additionally, no evidence has been present that the fusion polypeptide is capable of regenerating diseased liver tissue. For these reasons and those discussed in the previous office actions, the rejection is maintained. .

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER